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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/914,615 | 12/26/2001 | Paul Meers | TRA-016.01 | 9551 |

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| EXAMINER | |
|---|---|
| KISHORE, GOLLAMUDI S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1615 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/914,615 | MEERS ET AL. | |
| | Examiner | Art Unit | |
| | Gollamudi S. Kishore, Ph.D | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The RCE dated 9-7-07 is acknowledged.

Claims included in the prosecution are 1-7.

*Claim Rejections - 35 USC § 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Szoka (PNAS, 1978) in combination with either Gao (5,795,587) or Papahadjopoulos (6,071,533), optionally in further combination with Tikchonenke (Gene) of record.

Instant method claims are drawn to formation of liposomes wherein the active agent is complexed with a complexing agent; the method steps in claims 1 and 2 recite two variables. 1) the complexing agent is added to the emulsion in the second aqueous solution whereas the active agent is added in the first aqueous phase to form the emulsion (claim 1); 2) the complexing agent is added in the first aqueous medium to

form the emulsion and the active agent is added in the second aqueous medium to the emulsion.

Szoka teaches a method of preparation of liposomes. The method involves preparing a solution of a phospholipid in an organic solvent, mixing with an aqueous solution of the active agent to form an emulsion and evaporation of the solvent to form unilamellar liposomes. According to Szoka this method is valuable for the encapsulation of RNA or DNA. The sizes of the liposomes are between 120-300 nm. (abstract, Materials and Methods and page 4198). What is lacking in the method of Szoka is the addition of a complexing agent to the emulsion containing the active agent or addition of active agent to the complexing agent containing emulsion.

Gao teaches liposomal delivery systems in which the nucleic acid is complexed with a polycation. According to Gao such complexes are stable, capable of being produced at relatively high concentrations and retain the biological activity of the drug component over time in storage. Such liposomes have high transfection ability. The polycations include polylysine, spermine and spermidine (abstract, col. 4, line 66 through col. 5, line 8, col. 9, lines 40-55 and examples).

Papahadjopoulos discloses liposomal delivery system in which nucleic acid is complexed with a polycation such as spermidine, spermine and poly amino acids. According to Papahadjopoulos, surprising discovery of their invention is that the use of polycation provides a lipid-nucleic acid complex that remains capable of transfecting a cell in vivo even after a period of prolonged storage (abstract, col. 7, lines 9-40, col. 8, lines 20-28).

Tikchonenka while disclosing liposomally encapsulated DNA-spermine complexes teaches at lower concentrations of spermine, DNA assumes a compact toroidal shape and higher concentrations of spermine would result in aggregation. Tikchonenka further teaches that the average torus diameter is 0.1 microns, which is smaller than the average diameter of RPE liposomes (abstract, page 323, col. 2 through page 324, col. 2).

The addition of an aqueous solution containing a polycation such as polylysine or spermine or spermidine to the organic solvent-aqueous solution mixture containing an active agent such as a nucleic acid would have been obvious to one of ordinary skill in the art since the references of Gao, and Papahadjopoulos teach that the complex formed has a high transfection ability even after prolonged storage. Although Szoka does not teach the formation of the emulsion first with the complexing agent and then the addition of the active agent, it would have been obvious to one of ordinary skill in the art that a complex formation would occur whether the active agent is added to the complexing agent emulsion or complexing agent is added to the active agent containing emulsion since the complexation process is between an anionic agent and a cationic agent. It should be pointed out that the active agent and the complexing agent both being hydrophilic, will be sequestered in the aqueous medium and the liposome formation only occurs upon the removal of the organic solvent. One of ordinary skill in the art would be motivated to manipulate the amounts of the complexing agents to obtain a compact complex of smaller diameter so that the complex is encapsulated within the liposomes as taught by Tikchonenka.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Szoka does not teach the complexing agent. The examiner agrees and points out that the secondary references teach the complexing agents and the motivation to add the complexing agent. Applicant argues that Gao fails to teach encapsulation of the bioactive active complex comprising a bioactive agent. According to applicant, Gao teaches lipid/DNA complex by mixing an aqueous buffer solution of DC-Chol/DOPE liposomes and the resultant product is not an encapsulated DNA. This argument is not persuasive since the primary reference of Szoka teaches the encapsulation of DNA within the liposomes and Gao is combined for its teaches of high transfection ability of the complex compared to DNA alone and one of ordinary skill in the art would be motivated to encapsulate this complex in Szoka's liposomes because of this property. Applicant argues that Papahadjopoulos does not teach a method where polycation and nucleic acid are reacted in a water in oil emulsion. According to applicant, like Gao, Papahadjopoulos describes the method of preparation of lipid/DNA complex by simply combining an aqueous lipid suspension with an aqueous buffer mixture of plasmid DNA and that like Gao, no complexed bioactive agent is encapsulated in a liposomes. These arguments are not persuasive since Szoka teaches the ability of the liposomes to encapsulate DNA and Papahadjopoulos teaches the advantages of using the complex. Applicant further argues that nowhere does the examiner point to any teaching or suggestion of forming an emulsion prior to forming the complexed bioactive agent and that the examiner merely states that it would have been obvious that such reagents would react because of their opposite charge. Applicant

further argues that uncontrolled complexation occurs in aqueous solution and that as in Gao and Papahadjopoulos results in aggregates too large to subsequently encapsulate with a lipid to form small liposomes. This argument is not persuasive. First of all, claim 1 is drawn to bioactive agent and not to DNA. Secondly, as the reference of Tikchonenka indicates, that one can change the conditions to obtain a compacted complex with sizes of 0.1 micron, which is smaller than an average liposome.

3. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szoka in combination with either Gao (5,795,587) or Papahadjopoulos (6,071,533) and Tikchonenka as set forth above, further in view of Kim (5,723,147).

The teachings of Szoka, Gao, Papahadjopoulos and Tikchonenka have been discussed above.

Kim (587) discloses a process of preparation of liposomes in which the lipid in an organic solvent is added with an aqueous solution of an active agent, which in turn is added, with a second aqueous solution containing a cationic amino acid lysine. The organic solvent is then removed. Kim teaches various active agents including DNA and RNA (abstract, col. 6, line 62 and Examples). In essence, Kim teaches the addition of the active agent and the complexing agent by their introduction into the emulsion through two separate aqueous solutions. One of ordinary s

One of ordinary skill in the art would be motivated to add the active agent such as nucleic acid and the complexing agent through separate aqueous media to form a complex with a reasonable expectation of success since the reference of Kim shows its routine practice in the art. One of ordinary skill in the art would expect similar

complexation with a polycation such as spermine and the complex encapsulated within the liposomes.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that the complexing agent in Kim is not a polycation. Applicant further argues that the sizes of liposomes in Kim are bigger. The examiner agrees, but points out that Kim is combined for the teachings of adding two aqueous solutions and the reference of Tikchonenka shows that one can produce a compact complex using even a polycation such as spermine with a smaller diameter than an average liposomes and Szoka teaches smaller liposomes.

4. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tikchonenka as set forth above by itself or further in view of Kim (5,723,147).

The teachings of Kim have been discussed above.

Tikchonenka while disclosing liposomally encapsulated DNA-spermine complexes teaches at lower concentrations of spermine, DNA assumes a compact toroidal shape and higher concentrations of spermine would result in aggregation. Tikchonenka further teaches that the average torus diameter is 0.1 microns, which is smaller than the average diameter of RPE liposomes. The method of preparation of liposomes followed by Tikchonenka is that described by Fraley et al which is essentially the same as Szoka and Papahadjopoulos cited above (abstract, page 323, col. 2 through page 324, col. 2). In essence the method involves preparing a solution of a phospholipid in an organic solvent, mixing with an aqueous solution of the active agent and complexing agent to form an emulsion and evaporation of the solvent to form

unilamellar liposomes. Although it is unclear from Tikchonenka whether DNA and complexing agents are added separately as two aqueous solutions, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to manipulate the method of Tikchonenka to obtain the best possible results since they molecules are oppositely charged are expected to interact to form a complex if added in separate solutions. One of ordinary skill in the art would be motivated to add in separate solutions since the reference of Kim shows that two agents can be added separately.

The reference of Fraley et al which teaches that the method of preparation followed is that of Szoka is cited of interest (see experimental procedures).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK